UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,302	11/02/2000	Kurt Berlin	81587	4345

23685 7590 11/14/2002

KRIEGSMAN & KRIEGSMAN
665 FRANKLIN STREET
FRAMINGHAM, MA 01702

EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/14/2002

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/705,302	Applicant(s) BERLIN ET AL.	
	Examiner Cheyne D Ly	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/21/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' arguments in Paper No. 8, August 21, 2002, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Claims herein under examination are claims 1-50.

Response to Arguments

3. Claims 1-50 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is set forth as a new ground of rejection with respect to Claims 1-50.

4. It is reiterated that the Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering

are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

5. With respect to the "expert rules," Applicants argue that it is widely known and accepted that human knowledge about prediction and classification in any field can often be as a set of heuristics or "rules-of-thumb," therefore, would not require undue experimentation which is found unpersuasive because the Applicants' response and the specification does not set forth the necessary disclosure that would support the Applicants' argument. As defined by the Encyclopedia Britannica, heuristic is branch of computer technology dealing with "trial-and-error" or "exploratory" method of problem-solving; involves taking certain steps toward solution of problem and evaluating results as these steps are completed; implies use of intuition instead of formal techniques; opposite of algorithmic approach, which is precisely defined and structured; comes from Greek work heuriskien, meaning "to find out, to discover." Therefore, a definition, which includes the phrases "trail-and-error", or "exploratory," conveys that heuristic is experimental in nature. A method which is inherently heuristic would require sufficient guidance and direction in formulating "expert rules" to enable a person of ordinary skill in the art to make and use the invention without requiring undue experimentation.

6. Applicants discusses the importance of references listed on pages 11-14 where a large number of disease associated with a modified methylation patterned are identified. Therefore, it is assumed by the Applicant that because of the abundance of research literature that one of ordinary skill in the art could use the information from the references, without undue experimentation, to devise expert rules for identifying a disease based on a methylation pattern. Such argument is also found unpersuasive because currently the art of identifying a disease based

on a methylation pattern is comparable to one tossing a coin with a fifty percent chance to correctly determine, based on methylation pattern data, that a patient has myelodysplastic syndromes (MDS). According to the first reference on page 11, Aoki et al. cited a previous report by Uchida et al. that hypermethylation of the 5' CpG island of the $p15^{INK4B}$ gene occurred frequently in patients with MDS (16/32 [50%]) (Page 1403, Column 1, Lines 12-13). Therefore, a method that is based on data that is at most fifty percent accurate would require sufficient guidance and direction in formulating "expert rules" to enable a person of ordinary skill in the art to make and use the invention without requiring undue experimentation.

7. With respect to "selecting a type of disease or medical condition based on the methylation status...," and "ranked listing of diseases [...] based on the information about the methylation status [...]." Applicants argue that the disease types or medical conditions can be taken from any standard book for diagnosis on the basis of the methylation status which is found unpersuasive because diseases cited by references on pages 11-14, specifically Nosaka et al., used diagnostic criteria that are more than just methylation status. For example, leukemia is listed in the specification as one of the diseases that is found to be associated with methylation patterns. It has been reported that there are four clinical subtypes of adult T-cell leukemia-lymphoma and each subtype has its unique diagnostic criteria (Shimoyama M). The different set of criteria are critical for accurate T-cell leukemia-lymphoma diagnosis. Therefore, it is re-iterated with respect to "selecting a type of disease or medical condition based on the methylation status...," and "ranked listing of diseases [...] based on the information about the methylation status," the instant application lacks any amount of direction as to the practice of the process of "selecting a type of disease or medical condition based on the methylation status..."

The specification and response do not provide or suggest any parameters within which the selection is to be practiced, nor from which list the selection is being selected from. Further, the specification and argument do not provide or suggest any parameters within which the diagnostic criteria to each disease are being used in terms of ranking the disease. As such, claims drawn to the use of the select disease type or medical condition are not enabled.

8. Claims 1-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained with respect to Claims 1-50, as recited in the previous office action Paper No. 7, mailed March 07, 2002.

9. In regard to Claims 1, 14, 28, and 40 Applicants' argument has been considered but found to be not persuasive. The rejection is maintained because Claims 1, 14, 28 and 40 are vague and indefinite for failing to recite a final process step, which agrees back with the preamble. For example, Claim 1 is drawn to a method for guiding the selection of a therapeutic treatment for a patient, yet the claim recites a final step of generating a list of diseases or medical conditions in a computing device. Also, a list of diseases or medical conditions does not agree with the goal of the preamble of accomplishing the step of selecting a single therapeutic treatment for a patient. Claim 14 is drawn to a method of treatment, yet, nowhere in the claim is the step of treating a patient is accomplished. The step of generating a ranked list of diseases or medical conditions may be a precursor step to treating a patient. However, generating ranked list of diseases or medical conditions does not actually accomplish the active step treating a patient as administering a drug to address a specific disease or related symptoms would. Claims 28 and 40 are drawn to a system and a computer program for guiding the selection of a therapeutic

treatment for a patient. Similar to Claims 1 and 14, these claims do not contain the support for achieving the goals of the preamble of guiding the selection of a therapeutic treatment for a patient because they merely recite ranked list of diseases or medical conditions. Thus, the instant claims are unclear as to whether the preamble of the actual claim steps control the metes and bounds of the claims. In other words, would someone infringe the claims by simply performing the claim steps without performing what the preamble states? Clarification of the metes and bounds of the claims via clearer claim wording is requested. Claims which are directly or indirectly dependent from claims 1, 14, 28 and 40 also contain the above unclarity due to their dependence.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 2, 4 and 6-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barry et al. (US PN 6081786) taken with Ben-Yehuda. (December 1997).

12. Barry et al. discloses a method of providing patient information to a computing device that includes various knowledge bases. "For example, a first knowledge base may include a plurality of different therapeutic treatment regimens for a disease or medical condition. A second knowledge base may include a plurality of expert rules for selecting a therapeutic treatment regimen for the disease or medical condition. A third knowledge base may include advisory information useful for the treatment of a patient with different constituents of different therapeutic treatment regimens. A fourth knowledge base may include information about past therapies, such as how a patient has fared under previous therapies. A list (preferably a ranked listing) of therapeutic treatment regimens for a patient is generated in the computing device. Advisory information for one or more treatment regimens in the listing is generated in the computing device based on the patient information and the expert rules" (Column 2, Lines 47-64). Further, Barry et al. teaches the selection of therapeutic treatment regimens for diseases (or medical conditions) such as cardiovascular disease, lung and prostate cancer, and organic brain syndrome (Column 6, Lines 36-55). A method comprises of entering a user-defined therapeutic treatment regimen for disease or medical condition that is not included in said first knowledge base; generating in said computing device advisory information for said user-defined combination therapeutic treatment regimen (Claim 2). The patient information comprising gender, age, weight, CD4 information, viral load information, HIV genotype and phenotype information, hemoglobin information, neuropathy information, neutrophil information, pancreatitis, hepatic function, renal function, drug allergy and intolerance information (Claim 4).

The patient information including prior therapeutic treatment regimen information (Claim 5). The patient information includes prior patient information stored in a computing device (Claim 6). The advisory information includes warnings to take the patient off a contraindicated drug before initiating a corresponding therapeutic treatment regimen; and information clinically useful to implement a corresponding therapeutic treatment regimen (Claim 7). The computing device comprises a fourth knowledge base comprising patient therapeutic treatment regimen history, said advisory information including previous therapeutic treatment regiment information extracted from said fourth knowledge base (Claim 8). The disease or medical condition is a cardiovascular disease, a pulmonary disease, a neurologic disease, cancer, diabetes, a urinary tract infection, hepatitis or HIV infection (Claims 13-19). The drug dosage information is recommended and adjusted if necessary depending upon said patient information (Claim 21). Accessing, via said computing device, information for one or more therapeutic treatment regimens from a drug reference source (Claim 22).

13. However, Barry et al. does not specifically teach that the knowledge bases to comprise of methylation statuses at selected sites of the DNA in cells with a know disease or medical condition at selected sites of the DNA of a patient. Ben-Yehuda et al. teaches that methylation provides a better tool for monitoring the efficacy of IFNα treatment. Methylation analysis could pick up early signs of IFNα therapy failure and prompt an alternative mode of treatment, such as BMT (Page 4922, Column 2, Lines 22-26). Clearly, a skilled artisan would have been motivated to partake the concept emphasized by Barry et al. for providing patient information to a computing device that includes various knowledge bases by adding a knowledge base containing methylation statuses at selected sites of the DNA in cells with a know disease or medical

condition at selected sites of the DNA of a patient. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to add patient data concerning patient methylation status and TNFα treatment regimens provided by Ben-Yehuda et al. (Materials and Methods, Page 4919, Column 1 and 2) to the knowledge base of the method disclosed by Barry et al. for guiding the selection of therapeutic treatment regimens.

14. No claim is allowed.

15. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

17. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

18. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
11/13/02

ARDIN H. MARSCHEL
PRIMARY EXAMINER